^{19}F-Hyperpolarized Structures as Markers for the Improved Detection of Amyloid Plaques

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Purpose

Alzheimer´s disease is a neurodegenerative dysfunction which is one of the most frequent causes of dementia. The cause and progression of AD are only poorly understood. Because extracellular β-amyloid (Aβ) deposits, so called amyloid plaques, were postulated to be a fundamental cause of the disease, these structures are intensively investigated using various methods. As early diagnosis is a prerequisite for an effective treatment, techniques, such as MRI, enabling a sensitive detection of these distortions with high spatial resolution become increasingly important. It could be shown, that the application of substrates which specifically attach to β amyloid plaque, can effectively enhance the sensitivity for the in vivo detection in MRI measurements using signals derived from ^{19}F bound to these molecular labels. These nuclei provide an optimal contrast due to the lack of endogenous fluorine in living organisms. This approach is only limited by the low concentration of these markers that can be accumulated *in vivo*. Thus, a further amplification for ^{19}F MR signals in such substrates using hyperpolarization would help to significantly improve this important approach. Using Parahydrogen induced Polarization (PHIP) strongly enhanced MR signals can be generated. The initially produced ^{1}H hyperpolarization can be transferred to hetero nuclei such as ^{19}F, ^{31}P, or^{13}C.[1] ^{19}F Hyperpolarization is still only documented for a restricted number of substrates. However, it could already be demonstrated that imaging of hyperpolarized ^{19}F nuclei, using fluorostyrene as an exemplary representative is feasible[2]. Substrates such as diphenylethylen- or fluorinated, bisstyrylbenzene derivatives are known to selectively bind to β Amyloid plaques[3], from which one is exemplarily illustrated (figure 1).

Methods

In this study the feasibility of applying PHIP to a commercially available substance was investigated yielding a hydrogenation product which is structurally very closely related to 1,3,4,6-tetrafluoro-2,5-bis(4-hydroxy)stryrylbenzene indicated by the colored part of the illustrated molecule (figure1). As has been proven by MRI experiments such structures pass the blood brain barrier and specifically label the pathologic structures of interest[4]. Parahydrogen was transferred to the starting material at earth magnetic field using either standard ALTADENA conditions or an additional field cycling step. The hydrogenation reaction was performed with 50 % enriched parahydrogen (6 bar pressure) in the presence of a Rh(I) based catalysts.

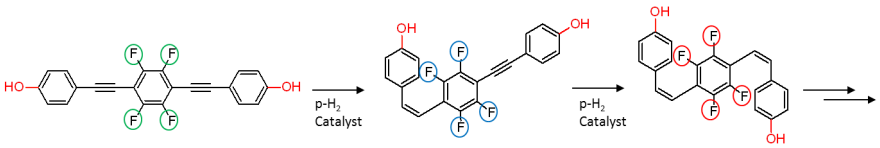

Figure 1: Schematic depiction of the parahydrogen transfer reaction. Substituents (OH-moieties) indicate the target system. Colored cycles illustrate the assignment of NMR signals presented in figure 2.

Results and Discussion

The ^{19}F spectra shown in figure 2 were detected after hydrogenation of 1,2,4,6-tetrafluoro-2,5-bis(phenylethinyl)benzen. The shown signals allow for an easy identification of the successive hydrogenation steps (figure 2). The first step produces an unsymmetrical molecule leading to two fluorine signals with an overall enhancement factor of 33 (blue). The second step, which corresponds to the target substrate, is completely symmetric with regard to the fluorine nuclei in this substance (red) and yields an enhancement factor of 3. It produces an enhanced in phase signal which, in particular, is very suitable for MRI experiments. Using field cycling, which allows for a more effective coupling between the transferred hydrogen nuclei and ^{19}F, the signal was inverted and the enhancement could be improved to a factor of 8.

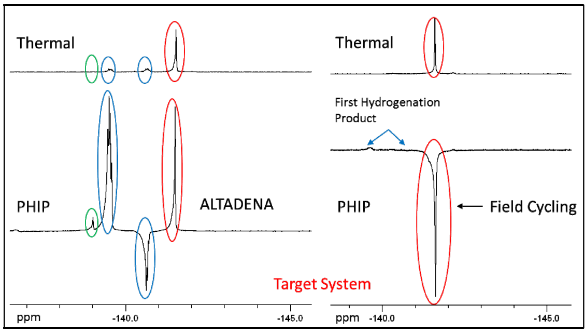

Figure 2: NMR-Spectra detecetd from para hydrogenation of bis-(phenylethynyl)benzene. Experiment performed using ALTADENA conditions (left) and additional field cycling (right).

Conclusion

These results, that could be achieved using just low technical effort, hold out the prospect of the possibility to hyperpolarize even the target system. An improved field cycling procedure to optimize the ^{1}H-^{19}F coupling for this system can further enhance the received signals for a better detection of amyloid plaques.

References: [1] Bhattacharya B et al. 2011, NMR Biomed 24 (8),1023;.[2]: Bommerich U et al. 2010, Phys Chem Chem Phys 12(35): 10309; [3]: Amatsubo T et al. 2010, Magn Reson Med Sci 9(3): 95; [4]: Higushi M et al 2005, Nat Neurosci, 8(4): 527.